Practitioner's Docket No.: 868_012 ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Noriaki KATO, Hiroshi NAGANO, Kaori TANIKO and Takahito JOMORI

Ser. No.: 10/587,320 Art Unit: 1618

Filed: May 10, 2007 Examiner: Nissa M. Westerberg

Confirmation No.: 4731

For: PROPHYLACTIC OR THERAPEUTIC AGENT FOR DIABETIC MACULOPATHY

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Commissioner for Patents
P.O. Box 1450
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicants request review of the final rejection in the above-identified application. No amendments are being filed with this request, which is being filed with a Notice of Appeal.

Claims 10-12, 14, 18, 20 and 21 are pending herein. Claims 10 and 18 are independent; claims 11, 12 and 14 depend from claim 10, while claims 20 and 21 depend from claim 18. The discussions below are directed to independent claims 10 and 18.

Claims 10-12, 14, 18, 20 and 21 were rejected under §103 over Mylari in view of Crary; and claims 10-12, 14, 18, 20 and 21 were rejected under §103 over Akita in view of Crary and Wani.

Mylari and Akita disclose that SNK-860 (Fidarestat), a compound of the present invention, has an effect on Diabetic Retinopathy or retinal edema. Wani discloses the linking of Diabetic Maculopathy (macular edema) and Diabetic Retinopathy (DR). During prosecution, evidence submitted by Applicants, including Declarations of Dr. Lorenzi

(submitted on June 26, 2009 and on February 26, 2010), caused the Examiner to acknowledge that Diabetic Macular Edema (DME) and DR are mutually different diseases and withdraw the rejections under §103 over Mylari and over Akita in view of Wani. The Examiner added a new reference, Crary, and made new grounds of rejections under §103. Crary discloses that the combination product of selenium and vitamin E has an effect on both of DR and macular edema in diabetic patients. Based on Crary, the Examiner stated that an effective agent for DR is suggested to be effective for DME and it is obvious that SNK-860, which has an effect on DR, would have an effect on DME. We will mention invalidity of this Examiner's theory mainly.

Here, the description by the Examiner that SNK-860 has an effect on DR is based on an experiment of rat model (Akita) or only one line description not based on experimental evidence (Mylari). On the other hand, the description by Applicants that SNK-860 is non-effective for DR is based on a human clinical study.

Against the Examiner's rejection, Applicants explained that a person of ordinary skill in the art would not think an effective agent for DR would be effective for DME by considering only Crary. The reason is as follows. The combination product of selenium and vitamin E in Crary is a food supplement, and vitamin E has a blood glucose-lowering effect and has an effect on diabetes (see Reference 2 listed below). On the other hand, SNK-860 is a medicament which is well known as ARI (aldose reductase inhibitor), and has no blood glucose-lowering effect. And there is no chemical relationship between these compounds. So, the combination product of selenium and vitamin E is completely dissimilar to SNK-860. Therefore, a person skilled in the art can understand easily that one could not apply the fact of the combination product in Crary to SNK-860. Furthermore, Applicants submitted several pieces of evidence appearing in Table 1 below. The evidence includes not only prior art, but also experimental data and more recent publications. This evidence proves that efficacy for DR and efficacy for DME are not correlated mutually. And the clinical treatment method of DR is different from that of DME. In this way, Applicants have proved that Examiner's theory is invalid and not reasonable.

Table 1 Clinical study in human

	Diabetic retinopathy	Diabetic macular edema
Calcium dobesilate	Effective (Ref. 3)	Non-effective (Ref. 4)
PKC-β inhibitor	Non-effective (Ref. 5)	Effective (Ref. 6)
Selenium and Vitamin E	Effective (Crary)	Effective (Crary)
SNK-860	Non-effective (Ref. 7)	Effective
EPA	Effective (Ref. 8)	Non-effective *

(* : The efficacy of EPA for DME is based on the data in the experimental monkey model.)

In addition, Applicants alleged that the present invention is not obvious from two viewpoints as follows.

(a) In experimental monkey model (the experiment in the Declaration of Mr. Kato submitted on July 16, 2008), SNK-860 was effective for DME exceedingly. But Epalrestat (EPA), which is only one ARI showing an efficacy for DR in human clinical study, was not effective, even though both SNK-860 and EPA belong to ARIs. Because only primates have macula in retina among animals, the experimental monkey model can reflect efficacy in human clinical study with certainty. In fact, SNK-860 was effective in both the experimental DME monkey model and the human DME clinical study. No one could predict the result of this experiment that SNK-860 was effective exceedingly, and, inversely, EPA was not effective.

(b) Furthermore, it is disclosed that ARI is hardly effective in human clinical study in general (Ref. 1). But SNK-860, which was not effective for DR in human clinical study, was effective for DME in human clinical study (the test example 4 in the specification). The result of this experiment is also unpredictable.

In response, the Examiner maintained the final rejection stating that "To establish a prima facie case of obviousness, only a reasonable expectation, not absolute predictability, of success is required" in the Advisory Action. But that reasonable expectation is not supported by the evidence of record because the record is replete with evidence establishing that there is no proper correlation in clinical trials between the DR and the DME of the claims. The Examiner must consider the rebuttal and arguments submitted by Applicants adequately and state explicit reasoning for maintaining final rejection (see MPEP 2142). The Examiner neglected this PTO requirement. In fact, the Examiner referred only to her theory mentioned

for a *prima facie* case of obviousness. It thus appears that the Examiner has ignored the KSR Guidelines (Federal Register, Vol. 75, No. 169, September 1, 2010).

In addition, Applicants made aforementioned assertions to overcome the *prima facie* case of obviousness or the "reasonable expectation" that the Examiner stated. The comparison data of experimental monkey model in the aforementioned Kato Declaration are appropriate for overcoming the *prima facie* case of obviousness or the reasonable expectation that the Examiner asserted. But the Examiner did not consider sufficiently the experimental data, and thus, the Examiner has also disregarded secondary considerations of patentability. This is also inconsistent with PTO examination procedure.

Now, Applicants have proved the existence of apparent mistakes of examination procedure. But Applicants will explain further about the non-obviousness of the present invention. The present claims' methods are restricted to *human* subject with diabetic *diffuse* macular edema. This is because the most important and difficult thing in the treatment of DME is the treatment of diabetic diffuse macular edema. While diabetic focal edema in DR written in Akita is easy to treat, diabetic diffuse macular edema is not easy to treat (Ref. 9). And it is said that ARI is hardly effective in human clinical study (Ref. 1). SNK-860 was effective for DR in a rat model but not effective for DR in human clinical study. Therefore, Applicants have clarified unpredictability of the claimed invention by restricting the claims.

Meanwhile, as the treatment of diabetic diffuse macular edema leads to the treatment of diabetic macular edema, Applicants use "DME (diabetic macular edema)", not "diabetic diffuse macular edema" in this argument.

In light of the foregoing, Applicants respectfully submit that all pending claims herein are patentable over the applied references. Accordingly, reconsideration and withdrawal of all grounds of rejection are respectfully requested.

Respectfully submitted,

November 22, 2010
Date

Stephen P. Burr
Reg. No. 32,970

SPB/CW/tlp

References: (all references have been previously submitted or cited in Office Actions, and thus are not filed herewith)
(1) MA Speicher, et al. "Pharmacologic therapy for diabetic retinopathy," Expert Opin Emerging Drugs 2003; 8: 239-250.
(2) Paolisso G, et al. "Daily vitamin E supplements improve metabolic control but not insulin secretion in elderly type II diabetic patients," Diabetes Care 1993; 16: 1433-1437.
(3) Ribeiro ML. et al. "Effect of calcium dobesilate on progression of early diabetic retinopathy: a randomized double-blind study," Graefe's Arch Clin Exp Ophthalmol 2006; 244:1591-1600.
(4) Haritoglou C et al. "Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomized, double-blind, placebo-controlled, multicentre trial," Lancet 2009; 373: 1364-1371.
(5) The PKC-DRS Study Group. "The Effect of Ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy," Diabetes 2005; 54: 2188-2197.
(6) PKC-DRS2 Group. "Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy,"Ophthalmology 2006; 113: 2221-2230.
(7) Investigational brochure of SNK-860 which was filed to Health, Labour and Welfare Ministry in Japan
(8) N Hotta, et al. "Diabetic retinopathy –Experimental and clinical approaches from polyol pathway- In: N Sakamoto et al., editors," Current concepts of aldose reductase and its inhibitions, Amsterdam: Elsevier Science Publishers B.V.; 1990. p.169-177.
(9) JM Lopes de Faria, et al. "Diabetic macular edema: Risk factors and concomitants," Acta Ophthalmol Scand 1999; 77: 170-175.

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